Chapter 5

Special problems of severe asthma in childhood

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Summary

Severe asthma accounts for a small proportion of all asthma in childhood, but consumes a disproportionate amount of healthcare resources, and leads to substantial morbidity and even premature death. Many different symptom patterns can lead to specialist referral with the diagnostic label problematic severe asthma.

First, there is a full review to exclude other diagnoses and important comorbid conditions. Next, standard management is optimised, ideally including a home visit. As a result, approximately half of the children, for whom basic management needs to be got right, are classified as having difficult asthma. We recommend invasive testing for severe therapy-resistant asthmatics in order to try to determine the pattern and distribution of inflammation; the extent to which the asthma is steroid-sensitive; and whether the child shows persistent airflow limitation (PAL). Therapeutic choices in these children are not evidence-based, and international collaboration is essential if this is to be rectified. Finally, we review the little that is known about mechanisms of severe asthma derived from paediatric studies.

Keywords: Airway inflammation, allergen, atopy, bronchoscopy, persistent airflow limitation, severe asthma

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Despite considerable advances in the understanding of asthma and mechanisms of inflammation in airway disease, particularly in adults with asthma, severe asthma in children is a poorly understood cause of significant respiratory morbidity worldwide. In the USA alone, although severe asthma accounts for less than 10% of all types of asthma in adults and school-age children, it is responsible for more than 60% of the health-related costs of asthma [1, 2]. There are no comparable data in pre-school children, although it is likely that severe pre-school wheeze consumes a disproportionate amount of healthcare resources. Whereas school-age children with mild and moderate asthma have been included in numerous interventional trials, treatment

studies targeting children with severe asthma are relatively few. Indeed, when the Childhood Asthma Research and Education (CARE) Network attempted to compare montelukast with azithromycin as add-on therapy for children remaining symptomatic despite prescribed treatment with inhaled corticosteroid (ICS) and long-acting β_2 agonist (LABA), the trial had to be abandoned as futile since only 55 out of 292 children could be randomised, the main reasons for exclusion being wrong diagnosis or failure to adhere to standard therapy [3]. As a result, the therapeutic options for children with severe asthma are based primarily upon expert opinion rather than evidence-based guidelines, and, with the exception of anti-immunoglobulin (Ig) E therapy (see later), are relatively unexplored.

A major impediment to the understanding of severe asthma in children has been the lack of a suitable definition appropriate for children of diverse ethnic/racial and sociocultural backgrounds. Definitions are often arbitrary and uncritically adapted from adult documents. Definitions of severe childhood asthma proposed by the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) third Expert Panel Report (EPR-3) and Global Initiative for Asthma (GINA) documents are based primarily on the severity and frequency of symptoms and the presence of airflow limitation [4, 5]. The severity level criteria and the stability of the phenotypes included in these guidelines have not been validated by longitudinal studies. Most of the children in the cross-sectional studies that have been performed exhibited highly symptomatic asthma treated with high levels of corticosteroids, but with only mild airflow limitation and air-trapping [6]. In 2000, American Thoracic Society (ATS) workshop participants published a consensus definition of severe asthma that introduced the concept that asthma severity might be related to the level of controller therapy necessary to attain or maintain adequate symptom control [7]. A modification of this definition is underway through the ongoing efforts of a European Respiratory Society (ERS)/ATS collaborative panel (as yet unpublished), and also the European Union (EU) Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) initiative [8]. A vital element missing from the original ATS definition is the importance of an appropriate period of observation on high-dose corticosteroids as a requisite for diagnosing severe asthma. This is a really important concept to which we subsequently return; severe therapy-resistant asthma can only be diagnosed after every effort has been made to ensure the basic management is correct, and after a period of observation on best protocol-driven standard treatment.

Phenotypic differences across the ages: how adults and children differ

General principles

A phenotype is defined here as follows: "a feature or, more usually, a cluster of features which leads to the separation of a specific group from the generality of wheezing children at a given time. These features may be in a single domain (for example, sputum cellularity) or in combinations of domains (for example, symptom patterns, sputum cellularity and airway physiology). Crucially, some useful action must result from the division, be it an approach to treatment or a fresh insight into disease mechanisms." This last point is the only justification for the approach. Temporal stability is required only insofar as it makes the phenotype useful in some way. Consideration should be given to what constitutes a real change in phenotype; a child with eosinophilic asthma may acquire secondary bacterial bronchitis or even a viral lower respiratory tract infection leading to a switch from an eosinophilic to a mixed cellularity or even a neutrophilic phenotype, but does this necessarily mean a change in underlying pathophysiology? Phenotyping may (in theory) be investigator-driven or data-driven. In the former, the investigator's experience (prejudice?) delineates phenotypes, *e.g.* sputum eosinophilia *versus* neutrophilia. In the latter, theoretically objective mathematical tools, such as latent class analysis, principal component analysis or systems biology approaches [9–11] are used to permit phenotypes to emerge from the data. However, this is not as objective as would be liked; the investigator's prejudices indicate what data is analysed.

Age-related phenotype of severe asthma

Steroid responsiveness was reported in a series of children who were a mix of difficult and severe therapy-resistant asthma [12]. This cross-sectional assessment included 102 children (mean $\pm$ SD age 11.6 $\pm$ 2.8 years); most (86%) were atopic and aeroallergen sensitisation was common, 59% were male and 23% exhibited persistent airflow limitation (PAL) as defined previously. The median ICS dose was 2 mg·day^{-1}, 35% were prescribed maintenance oral prednisolone and 14% had been intubated for asthma. 51% had additional or alternative diagnoses, although, in this cross-sectional study, it was not possible to determine whether or not they contributed to morbidity. Sensitisation to food allergens was common (24%); double-blind food challenges to confirm true food allergy were not performed. Three out of the 47 patients who underwent high-resolution computed tomography (HRCT) showed bronchiectasis. There were positive bronchoalveolar lavage (BAL) fluid (BALF) cultures in 19 (25%) out of 76, two-thirds with BALF neutrophilia. BALF cellularity was eosinophilic in 37%, neutrophilic in 44% and mixed in 16%. Bronchial mucosal biopsy specimens were eosinophilic in 53%, neutrophilic in 53% and mixed in 47%. 75% showed evidence of gastro-oesophageal reflux on pH study; in most cases, treatment of reflux did not appear to affect asthma control.

Corticosteroid responsiveness to either 40 mg prednisolone orally for 2 weeks or a single intramuscular injection of triamcinolone was assessed in 89 children by symptom score, spirometry, including bronchodilator responsiveness, and inflammometry (exhaled nitric oxide fraction ($F_{E}NO$) and sputum cytology, where available). Only 11% normalised all of these parameters after a steroid trial; partial responsiveness was common; it was not possible to convincingly predict steroid responsiveness from baseline data. From these results, it is clear that children with severe asthma are predominantly highly atopic; if anything, there is a male preponderance; and complete steroid responsiveness is unusual.

This is in marked contrast to adult studies. The European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA) study reported that severe asthma was dominated by females with less atopy and more neutrophilic inflammation [13]. The Severe Asthma Research Program (SARP) group also reported that there was less skin-prick test positivity in severe asthmatics [14]. Analysis of the Brompton cohort of severe adult asthmatics also demonstrated a female preponderance (75%), with 70% demonstrating evidence of atopy [15]. Of this cohort, 69% reported that their asthma first manifested before they were 20 years old. The relationship between childhood and adult phenotypes is unclear; recall bias is such that, without longitudinal studies, it is impossible to know what sort of problems the adult with severe asthma had as a child [16]. However, our data suggest that many children continue with a severe phenotype [17], and The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study also reported that, over a 2-year period, few severe asthmatics achieve control of their disease [18]. The Melbourne cohort study reported that nearly half of the children with severe asthma recruited at the age of 10 years showed chronic obstructive pulmonary disease (COPD) by the age of 50 years [19]. However, few of these children would have received current state-of-the-art treatment. There remains much to learn about adult and paediatric asthma phenotypes, and their interrelationships.

Recommendations of the 2009 World Health Organization panel

In 2009, an expert panel convened by the World Health Organization (WHO) met in Geneva (Switzerland) tasked with proposing a WHO definition of asthma severity and control, as well as criteria for describing exacerbations and their severity, which would be applicable in most circumstances to children and adults in low-, middle- and high-income countries [20]. Severe asthma was defined by the level of current clinical control and risks as follows: "uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)." The group defined three categories, which may overlap.

1) Untreated severe asthma. This is asthma which is untreated either because of failure to make the diagnosis or because basic access to care or medications (including spacers) is not available or affordable. This is an important group in low- and middle-income countries (LMICs) [21–23]; in addition to treatment access issues, there may be other factors, such as exposure to tobacco or biomass fuels, which exacerbate asthma [24]. Another issue may be the lack of locally applicable asthma guidelines, failure to apply basic principles of asthma treatment and lack of asthma education for families. It would be naive to suggest that medications alone are the answer, but equally wrong to think that the problem can be tackled without providing basic medications (as a minimum, prednisolone, the cheapest available ICS and β_2-agonists (usually beclometasone and salbutamol) and a plastic bottle to use as a spacer). Children in this category are also found in the parts of the developed world in which the costs of medications are prohibitive and reimbursement of healthcare costs is inadequate. It could be argued that children in whom compliance with the medication regimen is very poor despite access to medications could be placed in this category; in paediatric practice, we think it is more logical to place them in the difficult asthma category (below).

2) Difficult-to-treat severe asthma (or, in paediatric nomenclature, difficult asthma). These patients have asthma which is not apparently responding to treatment, but, often, when appropriate asthma management is instituted, the disease becomes controlled [25–27]. Problems may include adherence to treatment regimens, inappropriate or incorrect use of medication delivery devices, or adverse environmental circumstances [3, 28]. This category may be found in any setting. This category may also include children with unaddressed comorbid conditions, such as obesity, which impact asthma control, discussed in more detail later.

3) Treatment-resistant severe asthma (severe therapy-resistant asthma). Children in this category have severe asthma even with optimal management and after all conventional asthma medications have been given, or are controlled only with the highest level of asthma therapy, which has an unacceptable risk of side-effects. When making international comparisons, it is important to determine which medications are considered conventional and available. The therapeutic trials performed are different in countries where, for example, LABAs are not available compared with those in which they can be routinely prescribed. It follows that the definition may need to be modified in different countries, and it is essential that it should always be clear, particularly if comparisons between countries are being made.

It is important to distinguish the very different legitimate purposes for which these definitions may be used. Thus, in an LMIC, defining the prevalence of severe asthma may draw attention to the lack of diagnosis, basic medication or spacer devices, the need to improve healthcare delivery, the need to curtail the activities of the tobacco industry and the need for education about environmental hazards, such as biomass fuels. In a developed world setting, it may be used to define the rare asthmatics with severe therapy-resistant asthma so that the molecular and cellular mechanisms can be determined and novel therapies developed.

Finally, it is essential to realise that asthma is really a spectrum of clinical features rather than a precise diagnosis, rather like chronic renal failure, an end-point of many different processes. Thus the disease may show marked pathophysiological differences across the world. An obvious example is atopic sensitisation, which is common in childhood asthma in the UK. In Porto Alegre (Brazil), by contrast, asthma is usually nonatopic, and strongly associated with early respiratory viral infection [29]. It is known that genes do not exist in isolation but interact with the environment, and there are many obvious environmental differences across the world, although their importance is less well understood. Thus, when making comparisons between countries, it should not be assumed that asthma is the same in Colorado (USA) and Cape Town (South Africa).

Pre-school wheezing disorders

There are important developmental, as well as geographical, perspectives in paediatric asthma. Such evidence as exists pertains to severe asthma in school age. In infants and pre-school children

(defined as those aged 1–5 years), really severe asthma has been much less studied. Often, the pattern is one of viral exacerbations (which can be very severe) against a background of good baseline control [30], but pre-school children with chronic symptoms, often but not always with early-onset atopy, are not uncommon. Furthermore, the phenotype may change over time; episodic viral wheeze (EVW) may evolve into a multiple trigger pattern (MTW), and treatment with ICSs may lead to MTW appearing as EVW [31, 32]. A single study has looked at the results of a detailed investigation of pre-school wheezers with severe symptoms [33]. The studies, although invasive, yielded important unsuspected information, although outcome data showing benefit were not reported.

Still less is understood about wheeze during the first year of life [34]. It is clear that many infants who wheeze before their first birthday never exhibit further symptoms. Furthermore, severe episodes of obstructive airway symptoms in the first 2 years of life, but not the first year of life, were predictive of asthma at the age of 10 years [35]. It may be that one problem is the mislabelling of nonspecific respiratory noises as wheeze by parents and professionals [36–38]. It is likely that definitions in the pre-school years will have to be very different, and probably more exacerbation-based. Since so little is known about pre-school wheeze, and especially wheeze during the first year of life, such infants are not discussed further in the present chapter.

If real progress is to be made in understanding its natural history, severe asthma must be identified and studied early in childhood. More precisely, children must undergo thorough characterisation before being entered into mechanistic studies. The following section discusses the nomenclature and approach which are increasingly coming to be accepted in paediatrics. More details of the role of different measurements, such as spirometry, bronchial responsiveness and HRCT, can be found in recent reviews [26, 27, 39] and are summarised in table 1.

Definitions and clinical symptom patterns of asthma severity prompting referral to a specialist

This section describes children at the start of the investigative pathway, namely at the time of first referral to a paediatric asthma specialist and prior to the crucial step of ensuring that the basic management is correct, and thus prior to any period of observation on best protocol-driven standard treatment. Many of the approaches to severe asthma are common to adults and children, which may not necessarily be logical. The symptom patterns (most of which have arbitrary definitions and are based largely on adult criteria; as described earlier) which trigger the referral of a school-age child to an asthma specialist include the following. 1) Persistent (most days for at least 3 months) asthma symptoms prompting short-acting β_2-agonist use at least three times per week despite high-dose ICS (beclometasone equivalent of 800 $\mu g \cdot day^{-1}$) and trials of add-on medications (LABA, leukotriene receptor antagonist and oral theophylline at the low anti-inflammatory dose). 2) Type 1 brittle asthma (unstable high-amplitude swings in peak flow) [41]. Definitions and virtually all data are from adults. 3) Recurrent severe asthma exacerbations that have required either at least one admission to an intensive care unit with a life-threatening exacerbation or at least two courses of oral steroids during the previous year, despite the above therapy. 4) Type 2 brittle asthma (sudden and catastrophic attack on the basis of apparently good control) [41]; again, most data come from adults. 5) PAL: post-oral-steroid post-bronchodilator z-score of $\leqslant$ -1.96 for the forced expiratory volume in 1 second (FEV_1) using appropriate reference populations [42]. Others might prefer a definition based on the FEV_1/forced vital capacity (FVC) ratio. Hence, it should be noted that, unlike in adults, there is no accepted paediatric definition of PAL. 6) Requirement for treatment with alternate-day or daily oral steroids to maintain symptom control.

It would be quite wrong to assume that these various symptom patterns have the same pathophysiology or require the same therapeutic approach. The next section delineates how these children are further assessed, which is a prerequisite if: 1) a rational approach to treatment is to be found;

Table 1. The role of noninvasive measurements in the assessment of problematic severe asthma

Measurement	Role	Comment
Spirometry	Performed in everyone	Poor outcome measure Very little relationship to asthma severity Fundamental to diagnosis of PAL and assessment of acute BDR
Acute BDR	Performed in everyone	Anecdotally, a big response when prescribed LABA suggests poor adherence May not be present if lung function is normal at visit
Skin-prick tests, sIgE	Performed in everyone; correlation between skin tests and sIgE 76–83%	Review diagnosis in nonatopic individuals Quantify atopy (exacerbators) Guide allergen avoidance Look for food allergy (confirm double-blind with challenge) Diagnosis of SAFS [40]
Bronchial challenge test	Only if spirometry is normal or near-normal and diagnosis of asthma is in doubt	No evidence of response to challenge agent in a symptomatic child casts doubt on the diagnosis
HRCT	Selected asthmatics only	Perform if any diagnostic doubt Cannot distinguish asthma from OB, but can distinguish bronchiectasis No evidence of use as a biomarker in children
***F*eNO**	Performed in everyone; partitioned, if possible, to identify proximal and distal airways flux	Poor correlation with sputum eosinophilia If normal in a symptomatic child, review the diagnosis High alveolar *F*eNO suggestive of distal inflammation
Induced sputum	Performed on everyone with an FEV1 >70% pred; outcome studies awaited	Indication of type of inflammation (eosinophilic, neutrophilic, mixed or paucicellular)
Salivary or urinary cotinine	Performed on everyone	Passive smoke exposure Active smoking
Prednisolone (also cortisol) and theophylline levels	Performed on everyone prescribed either medication	Marker of adherence

The role of these measurements has been reviewed in detail elsewhere [27]. PAL: persistent airflow limitation; BDR: bronchodilator response; LABA: long-acting β_2-agonist; sIg: specific immunoglobulin; SAFS: severe asthma with fungal sensitisation; HRCT: high-resolution computed tomography; OB: obliterative bronchiolitis; *F*eNO: exhaled nitric oxide fraction; FEV1: forced expiratory volume in 1 second; % pred: % predicted.

and 2) mechanisms of disease are to be probed. It would be futile to lump together children symptomatic because of PAL with those whose problems would disappear if only they would take low-dose ICS correctly.

Label on entry: problematic severe asthma and how to move the diagnosis forward with appropriate investigations

Any child first referred to a specialist respiratory paediatrician meeting one or more of the six symptom or disease patterns described previously is termed as having problematic severe asthma [25]. This entry label comprises four groups, some of which may overlap, and all of which show age-related differences. These are: 1) wrong diagnosis (not asthma at all); 2) comorbid conditions

(asthma plus) [43]; 3) difficult asthma in which the problems can be addressed if the basics are right; and 4) severe therapy-resistant asthma in which the problems persist even when the basics are right. The clinical approach is summarised in figure 1.

Wrong diagnosis: not asthma at all

A full discussion of the differential diagnosis of wheeze in childhood is beyond the scope of the present chapter, but the number of possibilities is very high, and their prevalence varies with age and across the world. However, it should be remembered that age is not a bar to diagnosis of inherited disease; late diagnosis of congenital abnormalities (*e.g.* H-type fistula) and genetic conditions (*e.g.* cystic fibrosis (CF) and primary ciliary dyskinesia (PCD)) are well described. The diagnostic approach is summarised in tables 2–4, and in standard texts.

Comorbid conditions: asthma plus

These have been reviewed in detail elsewhere [43]. The five major issues to be considered in children are obesity with or without sleep apnoea, rhinosinusitis, gastro-oesophageal reflux, dysfunctional breathing and food allergy.

1) Obesity. Obesity, asthma and obstructive sleep apnoea (OSA) are all pro-inflammatory states, with complex interactions. Obesity may cause impaired exercise tolerance, leading to inappropriate escalation of asthma treatment; in adults, at least, it may cause a pauci-inflammatory polysymptomatic form of asthma [44], although whether this group is seen in children is less clear [45], and lead to steroid resistance [46]. In practice, clinicians should recognise that obesity *per se* is a cause of respiratory symptoms apart from asthma before escalation of asthma therapy.

2) Rhinosinusitis. The interactions between upper and lower airway inflammation are complex and debated [47]. Rhinitis is undoubtedly a source of morbidity, and should be treated on its own merits [48]. Likewise, OSA should be treated on its own merits; interestingly, OSA in children has been associated with neutrophilic lower airway inflammation [49], but whether treatment of either rhinosinusitis or OSA truly improves asthma is controversial.

3) Gastro-oesophageal reflux. Reflux is very common, may worsen respiratory symptoms, be itself worsened by respiratory disease or occur concurrently with asthma but not contribute to the severity of symptoms. There is no evidence from large studies that asthma is improved by treating symptomatic or asymptomatic reflux [50, 51]. Whether particular individuals may benefit, particularly symptomatic infants, may need to be decided by a therapeutic trial. In general, treating reflux in severe asthma has not been a helpful strategy in our experience.

4) Dysfunctional breathing. Vocal cord dysfunction, hyperventilation and other forms of dysfunctional breathing may mimic asthma, or, more usually, complicate the assessment of a known asthmatic [52, 53]. The disappearance of these symptoms when the child is asleep is a useful pointer, and asking the family to video an attack may also be useful. Evaluation by an experienced physiotherapist or paediatric clinical psychologist may be illuminating.

5) Food allergy. It is known that there is a high prevalence of sensitisation and allergy to food in severe asthma [54, 55]. What is not known is whether the relationship is causal or coincidental, nor how food allergy should influence treatment. Most would err on the side of caution in the treatment of the food-allergic asthmatic child.

Is the asthma difficult or severe therapy-resistant?

Numerous studies have shown that a comprehensive strategy targeted at the basics of asthma care eliminates problematic severe asthma in a child. What is not known is how best to sort out this problem in day-to-day practice. One possible protocol is summarised in table 5, and discussed in more detail later. In paediatrics, home and school visits, and detailed monitoring by community nurses,

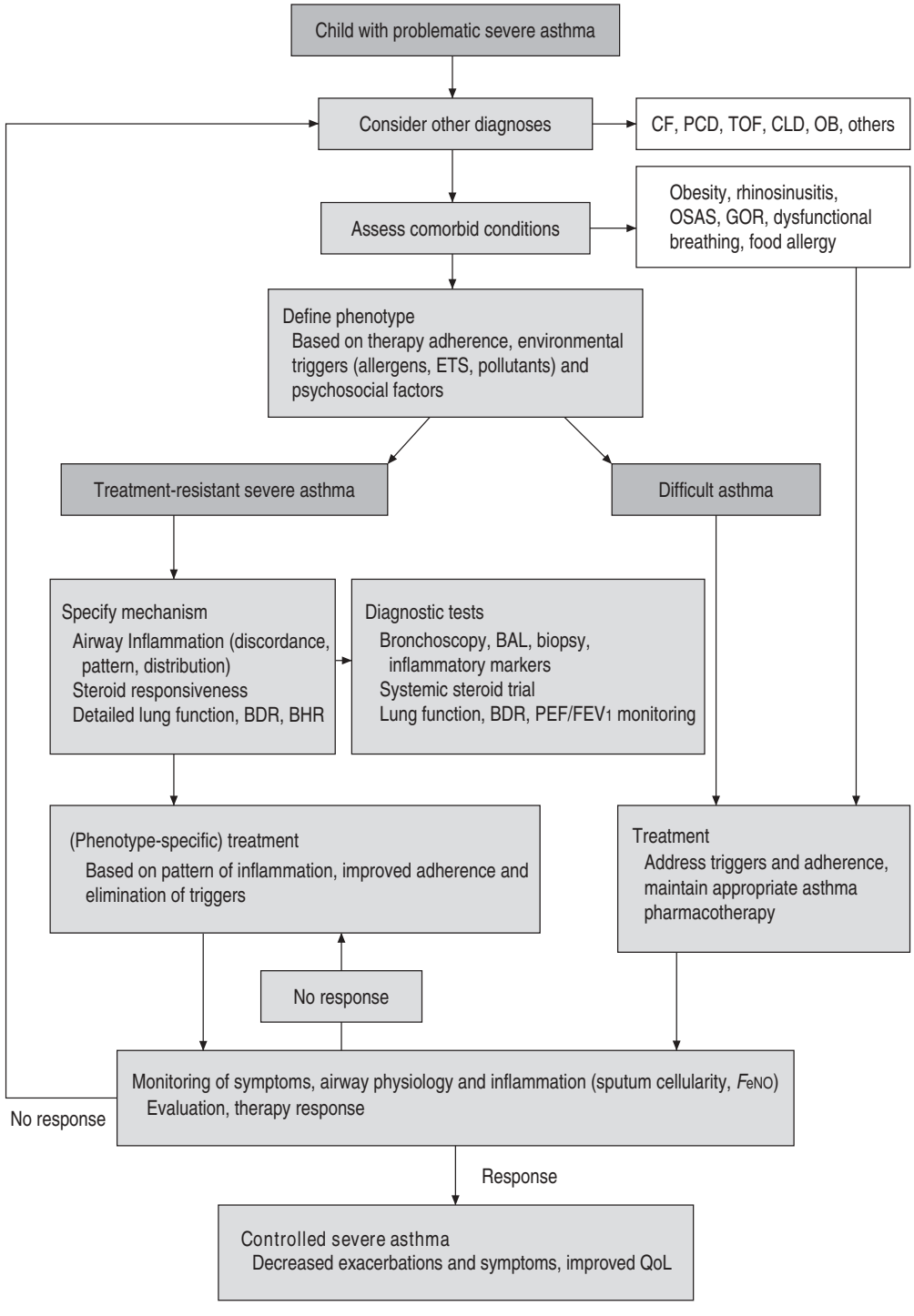

Figure 1. Summary of the approach to the child referred as having problematic severe asthma. CF: cystic fibrosis; PCD: primary ciliary dyskinesia; TOF: tracheo-oesophageal fistula; CLD: chronic lung disease; OB: obliterative bronchiolitis; OSAS: obstructive sleep apnoea syndrome; GOR: gastro-oesophageal reflux; ETS: environmental tobacco smoke; BDR: bronchodilator response; BHR: bronchial hyperresponsiveness; BAL: bronchoalveolar lavage; PEF: peak expiratory flow; FEV_1: forced expiratory volume in 1 second; F_{ENO}: fractional exhaled concentration of nitric oxide; QoL: quality of life.

Table 2. Points to seek in the history suggestive of an underlying serious diagnosis

Is the child/family really describing wheeze or some other noise? Parents often confuse stertor, a rumbling sound originating from the upper airways, with wheeze. The term wheeze is frequently used to describe nonspecific sounds. The use of a video questionnaire may be helpful.
Upper airway symptoms (snoring, rhinitis, sinusitis), which may be a comorbid condition, but also mimic asthma.
Symptoms from the first day of life. These are never due to asthma, and suggest a congenital malformation or PCD. They must be distinguished from viral respiratory tract infections acquired from family members in the first weeks of life.
Very sudden onset of symptoms, which suggests a foreign body. Direct questions about this possibility must always be asked.
Physician-diagnosed eczema in association with a parental history of allergy can be a clue that food sensitivities are present in a pre-school child with recurrent wheeze.
Chronic moist cough/sputum production, which should be distinguished from recurrent acute cough, for example with viral colds. The duration of symptoms before investigating chronic cough depends on whether there are associated symptoms, but the duration should not be allowed to exceed 8 weeks before investigation.
Worse wheeze or irritability after feed, worse lying down and vomiting are suggestive of gastro-oesophageal reflux, usually commonest in very young children.
Choking on feeds is suggestive of a neurological lesion or laryngeal cleft. If in doubt, an experienced nurse should witness feeding, and a specialist speech and language assessment considered.
Any feature of a systemic immunodeficiency. The acronym SPUR may be valuable (infection that is severe, persistent, with unusual organisms or recurrent).
Continuous, unremitting or worsening symptoms; asthma is a relapsing and recurrent disease.

A detailed history targeted towards other respiratory conditions is an essential first step in evaluating the child with problematic severe asthma. PCD: primary ciliary dyskinesia.

is the foundation of the approach [28]. In our hands, the big four areas to address are: adherence to therapy, environmental allergen exposure, tobacco smoke exposure, and psychosocial issues. Recent observational data suggest that nurse-led home visits may be useful [28].

1) Adherence to therapy. Doctors are notoriously poor at predicting which patients take treatment, and parents frequently overestimate adherence. Useful tools include: 1) measurement of serum medication levels (prednisolone and theophylline); 2) obtaining a list of prescriptions supplied (collecting a prescription does not guarantee adherence, but failure to collect guarantees non-adherence) [56]; and 3) assessment of whether there is a supply of easily accessible in-date

Table 3. Points to seek on examination suggestive of an underlying serious diagnosis in a child with problematic asthma

Digital clubbing, often missed because it is not sought in children, excludes asthma as the sole diagnosis
Weight loss or failure to thrive
Nasal polyps are almost pathognomic of CF in children (rare in paediatric PCD in our experience). May be seen in aspirin-sensitive teenagers with asthma
Upper airway: really severe chronic secretory otitis media, otorrhoea, enlarged tonsils and adenoids, and prominent rhinitis
Moist-sounding cough and palpable rattling on the chest (distinguish from transmission from the upper airway)
Unusually severe chest deformity (Harrison's sulcus or barrel chest), which does not exclude asthma, should prompt a diagnostic review
Unusual auscultatory signs; fixed monophonic wheeze, stridor (monophasic or biphasic), asymmetric wheeze or other auscultatory signs, and crackles, particularly if coarse
Signs of cardiac or systemic disease

Most children show no physical signs; however, none are found unless they are actively sought. CF: cystic fibrosis; PCD: primary ciliary dyskinesia.

Table 4. Differential diagnosis of problematic asthma and diseases that present as recurrent cough and wheeze

Upper airway disease: choanal stenosis (in infancy in particular), adenotonsillar hypertrophy, rhinosinusitis and post-nasal drip (controversial)
Congenital structural bronchial disease: complete cartilage rings, cysts and webs
Bronchial/tracheal compression: vascular rings, pulmonary and sling, enlarged cardiac chamber or great vessel, and lymph nodes enlarged by tuberculosis or lymphoma
Endobronchial disease: foreign body and tumour, including carcinoid
Oesophageal disease: gastro-oesophageal reflux, H-type fistula or laryngeal cleft, achalasia, eosinophilic gastroenteritis and familial dysautonomia
Swallowing problems: incoordinate swallow due to peripheral or central neurological disease.
Fixed airflow obstruction: obliterative bronchiolitis, usually post-infective in previously well children (adenovirus and *Mycoplasma pneumoniae*)
Causes of pulmonary suppuration: CF, PCD, persistent bacterial bronchitis and any systemic immunodeficiency, including agammaglobulinaemia and severe combined immunodeficiency
Others: bronchopulmonary dysplasia (should be apparent from the history), congenital or acquired tracheomalacia, pulmonary oedema secondary to left to right shunting or cardiomyopathy, idiopathic pulmonary arterial hypertension (presents with syncope, exercise breathlessness, haemoptysis and hypoxaemia)

These conditions need to be considered and excluded prior to escalation of therapy. CF: cystic fibrosis; PCD: primary ciliary dyskinesia.

Table 5. Royal Brompton Hospital Difficult Asthma Protocol

	Visit 1	Visit 2[#]	Visit 3[¶]
Clinical assessments	Asthma control test Nurse-led home visit Salivary cotinine School visit Access GP records Psychological assessment as appropriate	Asthma control test Assess symptoms, new peak flow diary	Asthma control test Assess symptoms, new peak flow diary Allocate as responder, partial responder or nonresponder to steroid Determine whether PAL present Individualised treatment plan based on pattern of inflammation
Physiological measurements	Spirometry, including response to β_2-agonist	Spirometry, including response to β_2-agonist	Spirometry, including response to β_2-agonist
Noninvasive inflammatory and other markers	Induced sputum F_{ENO} (variable flow) sIgE and skin-prick tests Measure prednisolone and theophylline levels if appropriate (HRCT not routine)	Induced sputum F_{ENO} (variable flow)	Induced sputum F_{ENO} (variable flow)
Invasive studies		Bronchoscopy, BAL, and bronchial biopsy Intramuscular triamcinolone pH study	

GP: general practitioner; PAL: persistent airflow limitation; F_{ENO}: exhaled nitric oxide fraction; sIg: specific immunoglobulin; HRCT: high-resolution computed tomography; BAL: bronchoalveolar lavage. [#]: if no improvement; [¶]: 4 weeks later.

medication in the home. Other adherence issues to be addressed include: 1) whether the child is supervised (often quite young children are left unsupervised by the carers) [57]; and 2) whether the child and family have an age-appropriate drug delivery device that is being used properly. Repeated education in the use of medication devices is frequently required [58]. In our series of problematic severe asthma, medication issues were thought to be important in nearly half of the children [28]. It is, of course, one thing to identify poor adherence and quite another to address it. However, few would think that the answer to poor adherence is the institution of experimental and potentially toxic therapy.

2) Allergen exposure. This is another controversial area, confounded by poorly performed studies, ill-considered meta-analyses and the inappropriate extrapolation of data to children with really severe asthma [27]. It is known that: 1) low-dose allergen exposure, even in school [59], can lead to deterioration of asthma control [60]; 2) allergen exposure and sensitisation are associated with increased severity of viral-induced exacerbations in school-age children [61]; 3) ongoing allergen exposure in sensitised adults leads to an interleukin (IL)-2- and -4-mediated state of steroid resistance [62, 63]; and 4) allergens may have non-IgE-mediated adverse effects [64, 65]. At least two studies have shown that a multifaceted education programme, including components of allergen avoidance, have long-lasting effects on asthma control [66, 67]. Thus, in children with ongoing severe asthma on high-dose medication, avoidance of relevant allergens seems reasonable. Furthermore, it is likely (but unproven) that families within whom the child has a real health problem are more likely to be diligent in allergen avoidance.

3) Tobacco smoke exposure. In adults, active smoking acts as an irritant, and also leads to a non-eosinophilic steroid-resistant form of asthma [68–71]. It is likely that passive smoke exposure has the same effects in children. Evidence of exposure from measuring urinary or salivary cotinine is common.

4) Psychosocial issues. These are common, whether causal of or caused by asthma is often unclear [72, 73]. Mechanistic studies have shown that airway inflammation is amplified by stress [74]. The clinical psychologist is a very valued and overworked member of the difficult asthma team; our approach is to treat asthma and psychosocial issues in parallel, rather than to attempt to determine which is causal.

This sort of detailed evaluation results in around half of patients with problematic severe asthma being classified as difficult rather than severe therapy-resistant [28]. Importantly, at least some of these investigations can be performed prior to referral, thus obviating the need for specialist evaluation. Even after referral, identifying difficult asthma reduces the need for invasive testing. In both cases, health costs are saved. This evaluation is not perfect, however. Undoubtedly some difficult asthmatics are incorrectly put into the severe therapy-resistant category because, for example, they can conceal their poor adherence.

These data have implications beyond individual care. Children with asthma that is not responding to treatment need to be carefully filtered in some way before being entered into randomised controlled trials or scientific studies. The filtering process may reduce numbers, but leads to better-focused studies. Otherwise, children not taking inhaled steroids will be enrolled into monoclonal antibody studies, which will then answer questions that are of no interest, or scientific studies, such as those investigating the mechanisms of steroid resistance or genes for asthma severity, will be diluted by those children, who could have well-controlled asthma if medications were administered.

Management of difficult asthma

There are few studies in children. Identifying a problem is important, solving it, in particular if behaviour is entrenched, is much harder. It is likely but unproven that repeated visits by community-based nurses to try to reinforce environmental measures is helpful. Occasionally, rehousing the family may be indicated, but more often the request for "a letter for the housing, doctor" is unjustified; we do not support rehousing so parents can smoke in greater comfort!

The literature on treatment at altitude in rehabilitation clinics is not definitive. Under extreme circumstances, and if the option is available, this may need to be considered. If adherence is an issue, asking the school to administer medications may help to ensure that the child gets treatment on at least 5 days per week. The input of a psychologist to address issues such as school refusal may help. In extreme cases of difficulty with parental reluctance to tackle the issues, child protection proceedings may need to be contemplated. There are usually no easy solutions, but clearly the avoidance of intensified and inappropriate medical therapy by identifying the problem is wholly beneficial.

Assessment of problematic severe asthma

There is even less evidence regarding how best to proceed in problematic severe asthma, and there is no international consensus. In particular, outcome data are lacking. Our consensus view is that the paediatrician should try to determine the following.

1) What is the pattern and distribution of any inflammation? Specifically, does the child have a discordant phenotype, with control of inflammation but ongoing symptoms [44], in which case further escalation of anti-inflammatory therapy seems illogical? In the child with multiple exacerbations, is there residual airway inflammation present between exacerbations, especially if control between exacerbations appears to be good? Alternatively, is there an alternate inflammatory pattern, for example dominated by neutrophils, which may respond to a less-orthodox treatment, such as a macrolides [75, 76]?

2) Does the child have true steroid-insensitive asthma, in which case alternative therapies should be sought? We accept that steroid-sensitivity is a spectrum, and we use an operational definition, namely the child's asthma is not sensitive to steroids at a dose that carries an acceptable risk of side-effects in that individual child. Alternatively, can the child's asthma be controlled on oral prednisolone at an acceptable dose?

3) Does the child have PAL? Clinicians should avoid toxic therapies in a futile attempt to improve lung function if there is no corresponding decrease in asthma symptoms.

The best means of answering these questions is unknown. There is a strong case for performing diagnostic bronchoscopy in such children, after due diligence with regard to prior assessment, as described previously, and with regard to the safety of the child [27]. Such bronchoscopy procedures, although safe, should be considered high risk, and should only be performed by really experienced bronchoscopists with senior anaesthetic support. During the bronchoscopy procedure, BAL and endobronchial biopsy can safely be performed, but, unlike at least under some circumstances in adults, transbronchial biopsy (TBB) cannot be justified due to the risk of pneumothorax and the unproven diagnostic yield [77].

What is the pattern of inflammation?

Discordant phenotypes

In some, but not all, asthmatics, levels of symptoms and inflammation correlate closely. The concept of discordant phenotypes permits rational treatment decisions [44]. The group data have largely been obtained in adults, but most clinicians have seen individual children who appear to exhibit discordance between inflammation and symptoms. If the child has a pauci-inflammatory polysymptomatic phenotype, there seems little point in giving ever-more-potent anti-inflammatory medication. Conversely, at least in adults, there seems to be a group with recurrent severe exacerbations who exhibit airway inflammation between exacerbations, but no symptoms. There is increasing evidence that treating this inflammation leads to a reduction in the number of exacerbations [78, 79].

Unusual patterns of inflammation

Although eosinophilic airway inflammation is most prevalent, some children have a picture of mixed cellularity or pure neutrophilia. The finding of airway neutrophilia should prompt a further review of possible causes, including passive smoke exposure, occult infection and gastro-oesophageal reflux. The treatment options have been reviewed elsewhere [27], and are summarised in tables 6 and 7.

Distribution of inflammation

Asthmatic inflammation may be compartmentalised. Proximal airway wall (endobronchial biopsy) and lumen (induced sputum and BAL) may show different patterns of inflammation [82], and it is unclear which is more important. Even more problematically, hyperpolarised magnetic resonance

Table 6. Proposed use of phenotypes to drive an individualised treatment plan

Phenotype/clinical problem	Treatment plan
Persistent chronic symptoms	Very-high-dose ICSs SMART regimen [80] Trial of low-dose oral corticosteroids (preferably alternate-day) Omalizumab if criteria met (see text) Steroid-sparing agent 5-LO inhibitor (zileuton)
Type 1 brittle asthma	Ensure no residual airway inflammation when well Appropriate dose of ICSs, plus high-dose LABA (formoterol) Consider a double-blind trial of continuous subcutaneous terbutaline [81]
Recurrent severe exacerbations	Ensure no residual airway inflammation when well (with appropriate dose ICSs) Optimise baseline control Optimise baseline lung function Ensure allergen exposure minimised Consider either or both of high-dose ICSs and leukotriene receptor antagonist with exacerbations
Type 2 brittle asthma	Ensure no residual airway inflammation when well (on ICSs) Provide injectable adrenalin for emergencies
Persistent airflow obstruction despite steroid therapy (see text)	Reduce treatment to minimum if obliterative bronchiolitis is the cause; treatment can often be stopped altogether Seek rare causes of obliterative bronchiolitis (*e.g.* rheumatological)
Prescription of alternate-day or daily oral steroids	Omalizumab if criteria met (see text) Steroid-sparing agent
Paucicellular airway cytology with persistent symptoms	Reduce dose of ICSs to lowest tolerated Consider SMART regimen Subcutaneous terbutaline with continued ICSs
Neutrophilic cytology	Reconsider the diagnosis and other causes of airway neutrophilia (gastro-oesophageal reflux, CF) Consider tobacco smoke exposure Low-dose oral theophyllines to accelerate neutrophil apoptosis Oral macrolides Consider a very cautious inhaled steroid taper (steroids inhibit neutrophil apoptosis)
Severe asthma with fungal sensitisation	Look for environmental exposures Oral itraconazole or voriconazole Look for bronchiectasis and evidence of ABPA

ICS: inhaled corticosteroid; SMART: Salmeterol Multicenter Asthma Research Trial; 5-LO: 5-lipoxygenase; LABA: long-acting β_2-agonist; CF: cystic fibrosis; ABPA: allergic bronchopulmonary aspergillosis.

Table 7. Evidence base for medication use beyond the guidelines

Medication	Evidence base
SMART regimen	No evidence of superiority over conventional therapy No studies in really severe paediatric asthma May theoretically help the poorly compliant
Macrolide antibiotics	Known immunomodulatory effects Proof-of-concept trials in adults with neutrophilic asthma No paediatric data in any form of asthma Good safety profile
Cyclosporin A	Little benefit in adults Case series only in children, suggesting benefit Careful monitoring essential
Methotrexate	Little benefit in adults Small open trials only in children, suggesting benefit Careful monitoring essential
Azathioprine	No evidence to recommend use in children or adults
Auranofin	Little benefit in adults No paediatric data
Immunoglobulin infusions	Limited evidence of benefit in adults and children
Subcutaneous infusion of terbutaline	Very limited evidence of benefit in adults and children Marked placebo effect Double-blind trial recommended if treatment is to be tried

These have been reviewed in detail elsewhere. SMART: Salmeterol Multicenter Asthma Research Trial.

imaging (MRI) studies in adults with asthma have identified persistent focal areas of hypoventilation in the asthmatic lung, supporting a heterogeneous pattern of inflammation [83]. In adult asthma, distal inflammation (identified by TBB) has been implicated in poor control [84–86], but there are no such studies in children. Indeed, the distal airways are very difficult to study in severe paediatric asthma. There are three possible approaches. TBB is not safe enough to be used as a research tool [77], and open lung biopsy is also too invasive. Partitioning nitric oxide production [87, 88] into proximal bronchial nitric oxide flux ($J_{br,NO}$) and distal alveolar nitric oxide concentration ($C_{A,NO}$) permits distinction between groups to be made [89], but the overlap is too great for decision-making in individuals. Finally, fractionating BALF may be helpful, as in the CF bronchoalveolar lavage for the evaluation of anti-inflammatory treatment (BEAT) study [90], but this approach has been used little in paediatric asthma. Sophisticated physiological testing, such as the lung clearance index [91–94], may be sensitive to distal airway disease, but is not able to determine the underlying cellular and molecular pathology.

Does the child have steroid-insensitive asthma?

It is known that steroid sensitivity is a spectrum, and true congenital steroid resistance [95] is very rare. Unlike in adults, there is no accepted definition of steroid resistance in paediatrics. Neither the dose of steroids nor the duration of therapy nor the parameters of response are agreed. Although a 10–14-day course of oral prednisolone at a dose of 1–2 mg·kg body weight^{-1} (maximum 60 mg) is conventional, there may be advantages to using depot triamcinolone, as a diagnostic trial only, since adherence is assured. There is a risk of tissue atrophy at the site of the injection [96], which needs to be discussed with the child and family. If triamcinolone is used, reassessment is performed 2–4 weeks later.

The parameters to be measured could include symptoms, FEV_1, bronchodilator responsiveness, F_{eNO} and sputum eosinophil numbers. In the absence of outcome data, recommendations are at the level of expert opinion. Possible criteria are summarised in table 8. It is obvious that missing from all conventional steroid trials is any effect on exacerbations, not least because, unless the

Table 8. Possible criteria for steroid responsiveness in children with severe asthma

Domain	Requirement
Symptom response	Asthma control test [97] rises to ⩾20 out of 25, or by at least 5 points
Lung function response	FEV_1 rises to normal (z-score of ⩾ -1.96) or by ⩾15% No residual bronchodilator response
Sputum eosinophil response (if paired induced sputum samples available)	Sputum eosinophil count normal (⩽2.5%) [98]
Nitric oxide response (if paired induced sputum samples not available)	$F_{ENO}^{\#}$ normal (⩽24 ppb) [99]
Composite domain: adult-type response	Asthma control test [97] rises to ⩾ 20 out of 25, or by at least 5 points, and FEV_1 rises to normal (z-score of ⩾ -1.96) or by ⩾15%
Composite domain: inflammatory response	Sputum eosinophil count normal (⩽2.5%) [98] and $F_{ENO}^{\#}$ normal (⩽24 ppb) [99]

Nonresponse: no improvement in any of the first four domains; partial response: one or two of these domains improve; complete response: all four of these domains normalise. FEV_1: forced expiratory volume in 1 second; F_{ENO}: exhaled nitric oxide fraction. #: measured at a flow rate of 50 mL·s^{-1}.

child has a viral infection during the steroid trial, this cannot be determined. Each of the various domains used can be criticised. Probably most important to children and caregivers are symptoms. However, symptoms may be over- or underestimated, and may be a poor guide to airway inflammation [44], which, if undertreated, may worsen virally induced symptoms [61]. Spirometric results are a notoriously poor outcome measure [4, 100, 101], even in children with severe asthma. There is little or no correlation between spirometric results and asthma severity, and even children with really severe asthma may show normal spirometric results. Since asthma is considered to be an inflammatory disease, and potent anti-inflammatory medications are used, an inflammatory response might be considered to be ideal. However, there are no paediatric outcome data validating this concept, nor, in these trendy days of patient-focused outcomes, is the concept of high-dose therapy to normalise airway inflammation likely to appeal to patients. It is probable that a multidimensional score will work best [102], but it is unclear what the components of this score should be. Furthermore, monitoring should ideally both aid control of day-to-day symptoms and also predict future exacerbations with enough of a lead time to permit intervention. The assessment and measurement of steroid responsiveness in children is another area in which much more work is needed.

Does the child have PAL?

Although the definition of PAL is reasonably straightforward (as described previously), and the concept of determining target lung function is logical, it is unclear how best to answer this question. Some form of steroid trial followed by acute administration of bronchodilator is logical, but the dose, duration and route of administration of steroid are not agreed. Spirometry following a prescribed arbitrary dose of prednisolone of 40 mg daily orally for the randomly chosen time period of 2 weeks does not determine optimal lung function [103]. As in so many areas, more work is needed.

Planning treatment: what are the problems?

With the exception of anti-IgE therapy (described later), there are no randomised controlled trials in paediatric severe asthma. Part of the problem is the heterogeneity of the disease, meaning that no one centre has sufficient patients who can sensibly be grouped for a trial. Another issue is that,

for reasons of toxicity and ethics, children are rarely included in trials of monoclonal antibodies or potentially hazardous procedures, such as bronchial thermoplasty. Thus treatment trials have to be on an individual basis, with monitoring of response, itself by no means easy when the disease fluctuates spontaneously and placebo effects are common.

The best evidence in severe paediatric asthma is for the anti-IgE monoclonal antibody omalizumab [104–106]. It is not clear from the trial data how many treated children genuinely had severe therapy-resistant asthma; however, many were prescribed an appropriate dose of ICS and one or more additional controllers. There are international differences in eligibility for this expensive and inconvenient treatment. Before prescribing this therapy, every effort must be made to correct reversible factors (described previously). Clinical trial data are convincing for the use of omalizumab in children aged over 6 years.

How should children with severe therapy-resistant asthma be monitored?

Studies in less-severe adult asthmatics have shown that monitoring sputum eosinophil count may be beneficial in terms of fewer exacerbations without the need to increase ICS dosage across the group [107]. The studies were predicated on the assumption that phenotypes (eosinophilic *versus* noneosinophilic) are stable over time. The only study in children with a mixture of difficult and severe therapy-resistant asthma failed to show benefit for this approach, measuring sputum eosinophils every 3 months [108]. A *post-hoc* analysis showed significantly fewer exacerbations for the eosinophil strategy group in the month following the sputum measurement [109], suggesting that more frequent measurements would perhaps have been beneficial. However, what also emerged from the study was that induced sputum cellularity showed marked variation over time, and, in addition, that *F*eNO and induced sputum eosinophil numbers could not be used interchangeably [110]. Even in the same child, the relationship between them was not constant over time. It has recently been suggested that *F*eNO should be used as a biomarker in its own right, rather than as a surrogate for sputum eosinophils. However a significant challenge to *F*eNO as a biomarker for asthma control is the fact that eosinophils *per se* do not express the inducible form of nitric oxide synthase (iNOS), as well as the marked complexity to the chemistry of nitric oxide and its reaction products in the human airway [111]. More work is needed in really severe paediatric asthma.

A different approach is the study of day-to-day fluctuations in lung function in order to disentangle asthma control and severity [112], as well as individual risk prediction based on previous hospital stays, summarised in [113]. Most of the data are from adults with relatively less-severe asthma [114].

Mechanisms of severe therapy-resistant asthma in children

Persistent asthma of childhood is characterised by infiltration of a mixed granulocytic pattern of inflammatory cells into the airway surface liquid. In a large bronchoscopy series in children with persistent asthma, airway eosinophils in BALF correlated primarily with the degree of allergen sensitisation, whereas BALF neutrophilia was surprisingly related not to infection but to duration of asthma [115]. Likewise, PAYNE *et al.* [116] have shown that airway eosinophilia may persist in some children with difficult asthma despite prednisone therapy. Data published in abstract form show that nearly 50% of children with severe therapy-resistant asthma show persistent sputum eosinophilia despite an intramuscular injection of triamcinolone. Activated eosinophils and neutrophils produce reactive oxygen and nitrosative species. Unquenched, reactive species injure the airways through the formation of toxic intermediate products (peroxynitrite) and lipid peroxidation of the airway epithelium [117]. Thus oxidative and nitrosative stress are plausible mechanisms linking inflammatory cell infiltration with airway epithelial dysfunction in severe asthma.

Children with both severe and non-severe asthma enrolled into the NIH/NHLBI SARP underwent bronchoscopy and BAL as indicated [118, 119]. It is likely that the group comprised a mix of difficult and severe-therapy resistant asthmatics. The sample was drawn primarily from children who received care at a large urban academic centre and was enriched with children of African-American race and ethnicity. Glutathione is the most important extracellular antioxidant, and is found in high concentrations in the reduced form (GSH) in healthy individuals [120]. BALF from children with severe asthma and airflow obstruction contained significantly more oxidised gluthathione (GSSG), and, likewise, contained markers of lipid peroxidation compared to healthy controls and asthmatics without airflow obstruction [121]. There is also a significant level of nitrosative stress in the airways of children with severe asthma. Compared to controls, children with mild-to-moderate and severe asthma showed significantly increased concentrations of nitrite, nitrate and nitrotyrosine in BALF despite treatment with ICS [112]. Ongoing studies will examine whether treatment with systemic corticosteroids (triamcinolone) might reduce this oxidative/nitrosative burden in severe asthma.

Apart from airway epithelial injury, airway oxidant-mediated stress in children with severe asthma is also associated with impaired alveolar macrophage phagocytic function, and thus may compromise innate immune function [122]. Indeed this finding supports the work of JUST *et al.* [115], who identified a higher than expected level of infection with capsular polysaccharide bacteria in the lower airways of children with asthma.

Inflammatory cytokines and chemokines released from effector T-lymphocytes and alveolar macrophages are important mediators of airways inflammation in persistent asthma. Studies that have been published recently describe the molecular phenotype of severe asthma in children based on supervised linear discriminant analysis [123]. In BALF, IL-13 and -6 differentiated children with asthma from controls, whereas growth-related oncogene (CXC chemokine ligand (CXCL) 1), RANTES (regulated on activation, normal T-cell expressed and secreted or CC chemokine ligand (CCL) 5), IL-12, interferon (IFN)-γ and IL-10 best characterised severe *versus* moderate asthma. However the most important finding in that publication was that the airway molecular phenotype of severe asthma did not exhibit a clear type-1 T-helper cell (Th) or Th2 pattern. This was also the case in a biopsy study [124], which showed no difference in IL-4, IL-5 or RANTES expression between a group of asthmatics (again, a mix of difficult and severe therapy-resistant asthmatics) and controls.

Synthesis of these BAL studies shows marked heterogeneity in the pattern of airway inflammation in children with severe asthma, perhaps more than might be expected based on the common theme of persistent atopy that has been identified in this disorder [6]. Further studies are acutely indicated in order to determine whether any one set of inflammatory markers is stable over time, and to examine the effects of important exposures, including high-dose corticosteroid and antileukotriene therapies, ambient air pollution and viral respiratory infections, in modifying the pattern of inflammation. The evidence today, however, best supports severe asthma in childhood as a highly complex disorder, differentiated from mild treatment-responsive asthma with unique molecular patterns of inflammation. Future therapies are likely to be based on children identified with specific biomarkers, and targeted at individual pathways.

Studies on airway remodelling in really severe asthma have established that reticular basement membrane (RBM) thickening is an early feature [125, 126], and does not seem to be related to the duration of asthma, treatment or any inflammatory marker. The structure of the thickened RBM is ultrastructurally the same as in normal subjects [127]. Airway smooth muscle is also increased in really severe asthma, correlating with the acute bronchodilator response to β_2-agonists [128]. Whether remodelling is protective or harmful is not established [129], nor is the relationship between features of remodelling, inflammation and asthma severity. The lack of noninvasive biomarkers for remodelling is a major problem; unlike in adults [130], HRCT results correlate poorly with airway biopsy findings in children [131], and, although breath condensate leukotriene levels and exhaled nitric oxide [132] have been reported to associate with remodelling in cross-sectional studies, no technique has been used as a biomarker longitudinally.

Another challenging growth area is molecular microbiology, relying on detection of bacterial RNA (16S ribosomal RNA (rRNA)) rather than culture. A recent study [133] has shown that the lower airway, far from being sterile, as was conventionally thought, contains a richer bacterial flora than the intestine. Children with severe therapy-resistant asthma, as defined previously, were found to have a different flora, specifically more *Proteobacteria* and fewer *Prevotella* species. Interestingly, the Copenhagen Studies on Asthma in Childhood (COPSAC) data [134, 135], using much-less-sophisticated methods (conventional upper airway bacterial culture), showed associations between early-onset wheeze and positive upper airway culture, and between exacerbations of wheeze and positive culture. The significance of these findings is unclear, but interpretations include: 1) asthma, like duodenal ulcer, is a bacterial disease; 2) the 16S rRNA findings reflect the effects of treatment with ICS; and 3) both asthma and the altered flora are a manifestation of an underlying defect in mucosal immunity. This is another area in which further research is essential. Overall, ethical constraints, including the virtual impossibility of recruiting normal paediatric controls, means that there are far fewer mechanistic studies in children than in adults.

The future: where from here?

It is obvious that there are huge gaps in knowledge of the mechanisms of severe therapy-resistant asthma, and there is no evidence base for recommending treatment. One of the few noncontroversial statements is that severe therapy-resistant asthma is a heterogeneous disease, and, from that, it seems likely that lumping everyone with nightmare asthma together will only lead to confusion. Therefore, it follows that international cooperation is needed, assessing problematic severe asthma with uniform protocols. Therefore what is needed is as follows: 1) agreed definitions, for example as to what constitutes an exacerbation, what constitutes steroid responsiveness and how it is measured, and how to determine whether PAL is present; 2) agreed protocols for differentiation of difficult from severe therapy-resistant asthma; 3) agreed phenotype-driven treatment protocols, preferably in the context of randomised controlled trials; 4) sharing of, in particular, invasively obtained samples, such as BALF and endobronchial biopsy specimens, for focused mechanistic studies; 5) more rigorous monitoring, particularly during the observation period, when basic management has been optimised, and also of changes in phenotype over time; 6) better biomarkers, in particular to predict treatment response, for following airway wall structural changes and monitoring therapy; and 7) cohort studies of properly characterised children with severe therapy-resistant asthma in order to determine important genetic mechanisms and gene–environment interactions. However, the key issue remains that, first and above all, if the asthma appears difficult, ensure that the simple things are being done correctly!

Statement of interest

W.G. Teague receives speaking fees from Merck/Schering-Plough that exceed 10,000 US$ annually.

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